REMARKS

This submission is in response to the final Office Action mailed October 16, 2006. Claims 1-41 are pending. Claims 2-9 and 23-39 have been withdrawn from consideration by the Examiner. Claims 1, 10-22 and 40-41 stand rejected. The Examiner has also maintained the provisional non-statutory double patenting rejection based on copending U.S. Patent Appln. Serial No. 10/256,283.

Claims 1, 11 and 22 are amended herein. Support for the claim amendments can be found, for example, in original Claim 10, Paragraphs 19, 20 and 24 and Examples 2-3 of the Specification. No new matter has been introduced by way of this amendment. Reconsideration is respectfully requested.

I. Rejections under 35 U.S.C. § 102(b)

Claims 1 and 10-22 stand rejected under 35 U.S.C. § 102(b) as anticipated by WO/24396 to Collier et al. ("Collier"). According to the Examiner, Collier allegedly teaches a composition comprising an NMDA receptor antagonist (e.g., eliprodil and ifenprodil) with a preservative (e.g., benzalkonium chloride) in amounts ranging from 0.01% to 5% by weight, preferably 0.01%. Applicants traverse the rejection and respectfully request reconsideration.

It is axiomatic that in order for a reference to anticipate a claim under 35 U.S.C. § 102(b), it must disclose *each and every limitation* of the claimed invention. *Dana Corp. v. Am. Axle & Mfg., Inc.*, 61 USPQ2d 1609 (Fed. Cir. 2002). Applicants submit that the amendments submitted herewith preclude a potential determination that Collier anticipates the claimed invention. Independent claims 1, 11 and 22, as amended herein, require specific NMDA receptor antagonists which are not disclosed by Collier. Specifically, Claim 1 requires NMDA receptor antagonists selected from the group consisting of: ketamine, dextromethorphane, dextrophan, dextropropoxyphene, ketobemidone, budipine, kynurenic acid, 1-hydroxy-3-aminopyrrolidin-2-one, spermine and spermidine. Support for this amendment can be found at Paragraphs 19 and 20 of the specification. Additionally, independent Claim 11, as amended, requires a preservative selected from the group consisting of: benzalkonium chloride, chlorhexidine, imidurea, alpha tocopherol, and EDTA. Support for this claim amendment can be found, for example, at paragraph 24 of the

specification. Additionally, the claims require an "anesthetically or analgesically effective amount" of the claimed NMDA receptor antagonist, another limitation not present in Collier.

Applicants submit that Collier is directed to particular formulations of certain glutamate antagonists which are not claimed by the present invention. Applicants note that similar amendments were made in copending Appln. Serial No. 10/256,283, which resulted in the Examiner overturning a previous anticipation rejection based on Collier. (*See* Serial No. 10/256,283 Office Action, Dated 11/6/2006 at 2.).

Based on the foregoing, in addition to Applicants' previous arguments of record, Applicants submit that the formulations in Collier do not anticipate the claimed invention. Accordingly, Applicants respectfully request the rejection be withdrawn.

II. Rejections Under 35 U.S.C. §103(a)

Claims 1 and 10-22 stand rejected as unpatentable under 35 U.S.C. 103(a) over GB 1330878 to Bristol Myers Co. ("BM") in view of U.S. Patent No. 6,638,981 to Williams et al. ("Williams"). According to the Examiner, BM allegedly teaches a composition of ketamine and benzethonium chloride. The Examiner relies on Williams to allege that benzalkonium chloride is an equivalent to benzethonium chloride. Further, the Examiner concedes that the references teach different dosage amounts for ketamine and benzalkonium chloride, however, the Examiner alleges one skilled in the art would be able to determine the claimed dosage amounts. Applicants respectfully traverse the rejection and request reconsideration.

A. The Examiner Has Not Presented a *Prima Facie* Case of Obviousness

To establish a *prima facie* case of obviousness, the Examiner must establish that: (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference teaches or suggests all the claim limitations. *See* MPEP §§ 706.02(j) and 2143. The proper inquiry is "whether there is something in the prior art as a whole to suggest the *desirability,* and thus the obviousness, of making the combination." *In re Fultion,* 391 F.3d 1195 (Fed. Cir. 2004).

i. Williams Fails to Show Equivalence Between Belzalkonium Chloride and Benzethonium Chloride

Applicants respectfully submit that a *prima facie* case of obviousness has not been established. Specifically, the Examiner's assertion that Williams "demonstrate benzalkonium chloride as a functional equivalents to benzethonium chloride" is misplaced. The Examiner's entire basis for asserting equivalence between benzalkonium chloride and benzethonium chloride is the following statement in Williams, a patent directed to topical application of anesthetics:

> Examples of preservatives include, but are not limited to, quaternary amines, such as quaternium 15, *benzalkonium chloride*, cetrimide, *benzethonium chloride*; and imidizolidinyl urea; organic acids, such as sorbic acid, p-hydroxybenzoic acid, and benzoic acid; parabens, such as methyl paraben and propyl paraben; alcohols, such as benzyl alcohol and isopropyl alcohol; phenols, such as triclosan, chlorhexidine, and thimerosal; . . .

(Williams col. 15, ll. 53-64) (emphasis added). Such a statement does not alone support a finding of equivalence between the two preservatives for a composition comprising an NMDA receptor antagonist. Indeed, such a conclusion completely eviscerates the invention, which highlights the difference between these two preservatives as discovered by the Applicants. The Examiner has entirely overlooked the basis of the invention, namely that benzalkonium chloride and benzethonium chloride have surprising differences. While the compounds may appear to be similar, the Applicants' invention is based on the discovery that they are not functionally equivalent, despite the long time belief that they are functional equivalents. The M.P.E.P. provides guidance for this exact situation: "In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on . . . the mere fact that the components at issue are functional or mechanical equivalents." M.P.E.P. § 2144.06; *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958). The Examiner's reliance on an assertion that the two preservatives are "functional equivalents" is in direct conflict with the guidance set forth in the M.P.E.P. Thus, the Examiner has failed to provide the requisite prima facie case of obviousness.

Assuming *arguendo,* that Williams did show equivalence between benzethonium chloride and benzalkonium chloride, which the Applicants do not concede, the Examiner points to no motivation to combine Williams with BMC, an important requirement to properly find obviousness.

See M.P.E.P § 2143.01. Of course, as noted above, the very basis of the invention is that benzethonium chloride and benzalkonium chloride are not equivalent, despite common belief to the contrary.

B. Assuming the Examiner Properly Showed Obviousness, Unexpected Results Are Shown

Even assuming that a *prima facie* case of obviousness has been established, which Applicants do not concede, Applicants have provided unexpected results to rebut any *prima facie* case. The Examiner does not appear to take direct issue with the data submitted to illustrate Applicants' invention (*See* Declaration of Donna Madden, submitted pursuant to 37 C.F.R. 1.132 on July 7, 2006; Examples 2-3 of the Specification). However, this data lends strong support to the invention proffered by the Applicants, namely that in compositions of NMDA receptor antagonists, the choice of preservative can have a significant impact on neurotoxicity. Furthermore, it is unclear how the Examiner can reject a scientific conclusion reached by Applicants as a result of the data submitted. Applicants respectfully submit that the Examiner has no basis for rejecting Applicants' scientific data of unexpected results. *See, e.g., In re Coordinated Pretrial Proceedings In Antibiotic Antitrust Actions*, 498 F.Supp. 28, 33-34 (E.D. Pa. 1980) (citing *Charles Pfizer & Co. v. F. T. C.*, 401 F.2d 574, 589 (6th Cir. 1968) for the proposition that "[t]he Patent Office must rely upon the information furnished by applicants since it has no testing facilities of its own"). Quite notably, "[in comparing the [studied] ketamine formulations, the greatest incidence of single neuronal degeneration was observed with the formulation containing ketamine in benzethonium chloride. This incidence was up to four-fold greater than that of ketamine containing benzalkonium chloride and two fold greater than observed with saline alone." (Declaration of Donna Madden ¶ 14, submitted pursuant to 37 C.F.R. 1.132 on July 7, 2006).

It appears that the central issue relating to the submitted data is the Examiner's disagreement with Applicants' use of the term "without significant neurotoxicity" throughout the claims. Specifically, the Examiner appears to conclude that this term is unclear in providing sufficient guidance as to how to ascertain what level of reduced neurotoxicity is required. Therefore, to effect additional clarity to the claims, Applicants amend the claims herein to alleviate the Examiner's concerns for potential ambiguity arising from the claim terms. Specifically, the independent claims

now require that the composition does not cause any significant neurotoxicity, and further, that the level of neurotoxicity is comparable to that of sterile water when administered. Support for this amendment can be found, for example, at Paragraphs 81, 94, 96, 101, 103, 120.

Applicants respectfully submit that the amendments and arguments provided overcome the obviousness rejection and place the claims in condition for allowance. Accordingly, Applicants request that the rejection be withdrawn.

III. Double Patenting Provisional Rejection

Claims 1 and 10-22 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over copending application 10/256,283. Since the rejection is provisional because the allegedly overlapping claims have not yet been patented, to the extent that claim scope overlaps in any patented case, Applicants will agree to submit a terminal disclaimer at such necessary time.

IV. Conclusion

Therefore, in view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: February 28, 2007

Respectfully submitted,

By Sandra Lee

Sandra S. Lee
Registration No.: 51,932

Jennifer Cozeolino
Registration No.: 59,021

Baker Botts L.L.P.
30 Rockefeller Plaza
44th Floor
New York, NY 10112-4498
(212) 408-2500
(212) 408-2501 (fax)

Attorneys/Agents For Applicant